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Acute Neurological Issues in Pregnancy and the Peripartum

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Abstract

Acute neurological diseases requiring hospitalization are relatively rare in women of childbearing age. However, during pregnancy and the postpartum period, several diseases increase in prevalence. Some are unique to the pregnant/postpartum state including preeclampsia and delivery-associated neuropathies. Others, although indirectly related to pregnancy, such as cerebral venous thrombosis, ischemic stroke, and intracerebral hemorrhage, increase in frequency and carry considerable risk of morbidity and mortality. In addition, treatment options are often limited. This review discusses the diseases more commonly seen during pregnancy and the postpartum period, with a focus on emergent neurological diseases and their management. Interventional therapies will also be discussed.

Keywords

headache disorders, myasthenia gravis, neuromuscular diseases, stroke, cerebrovascular disorders, pregnancy

Introduction

Although acute neurological diseases requiring hospitalization are rare in young women, several are unique to pregnancy and the postpartum period. The average age of pregnancy has increased from 24.6 to 27.2 in the past 30 years, increasing pregnancy-associated complications such as eclampsia, gestational diabetes, and hypertension.[1,2] Many of these neurological diseases can lead to devastating complications if not recognized early. Some, like preeclampsia, are easily recognized by obstetricians and are managed without significant neurological input unless seizures develop. Others are relatively "benign," such as femoral neuropathy, but should be recognized by neurohospitalists as they are often reasons for consults. Some diseases such as cerebral venous thrombosis (CVT) and pseudotumor initially present with nonspecific symptoms such as headache. However, headache is a common complaint in pregnant women and distinguishing the benign headache from one that is a sign of serious disease is often not considered until serious neurological complications develop. The pregnant woman is vulnerable in that many medications and diagnostic evaluations are avoided due to concerns of causing harm to the fetus. As neurological diseases contribute to approximately 20% of maternal deaths,[3] it is critical that neurohospitalists identify these at-risk patients. In this review, we will discuss several of the more common conditions associated with pregnancy, and emphasize the important differential diagnoses for diseases that have higher incidence in pregnancy, such as cerebral venous thrombosis and stroke, that can lead to significant morbidity and mortality in women during pregnancy and the postpartum period.

Stroke

Strokes, both ischemic and hemorrhagic, are a major contributor to morbidity and mortality during pregnancy and the puerperium. The physiologic and hemodynamic changes that occur in pregnancy promote a state of relative hypercoaguability, increased cardiac burden, and altered vascular tone in order to meet the physiologic demands of the growing fetus and reduce hemorrhage during delivery.[4] The overall incidence of ischemic stroke during pregnancy is low (3.5-5 per 100 000 pregnancies in the developed world), with the majority of these events occurring late in pregnancy and particularly in the postpartum period.[4,5] However, when considering stroke in the young as a broader group, it should be noted that strokes related to pregnancy accounted for 12% to 35% of events in this otherwise low-risk population.[4] The risk of recurrent stroke in subsequent pregnancies is of primary

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concern to patients and is a complex issue. The risk of recurrent stroke has not been reported as increased by some investigators.[6] However, others have identified an increased risk of stroke both with subsequent pregnancies and later in life in the subset of women with a diagnosis of preeclampsia during pregnancy.[7,8]

The etiology of stroke in pregnant women generally mirrors that of stroke in other young patients with the exception of the added risk that pregnancy-induced physiological changes and preeclampsia appear to confer. A nationwide inpatient sample analysis reported that preeclampsia, which is discussed elsewhere in this review, is associated with a 4-fold increase in stroke during pregnancy.[9] Hypertension, which is associated with both ischemic and hemorrhagic strokes, is a primary feature of preeclampsia and this study, along with others, may indicate a need for increased vigilance in hypertension management in these patients.[10] Hypercoaguable disorders are a concern for stroke in the young and can be related to both venous and arterial thromboses. Pregnancy, in and of itself, is a state of induced hypercoaguability which may facilitate the development of venous thromboemboli in a susceptible individual.[11] Paradoxical embolism related to the presence of a patent foramen ovale (PFO) may be facilitated by both the coagulation profile changes as well as by the hemodynamic changes such as increased venous stasis.[11] Peripartum cardiomyopathy is a rare complication of pregnancy in the developed world, but can carry a significant morbidity and mortality including cardioembolic stroke and severe progressive heart failure requiring transplant.[11] It is characterized by symptoms of heart failure related to left ventricular systolic dysfunction in women with no previous history of cardiomyopathy, and like many of the complications of pregnancy, may be identified in the postpartum period following an uncomplicated pregnancy and delivery.[11]

The diagnosis of stroke is considered in patients who present with acute onset of focal neurological changes in the absence of an alternative etiology. Additionally, and more rarely, patients present with nonfocal symptoms including headache and altered consciousness. Seizure may complicate the presentation and this appears to be more common in patients presenting with venous thromboses and subsequent venous infarctions.[4,12] The initial task for the clinician is to distinguish stroke from stroke mimics and, if stroke, to differentiate between ischemic and hemorrhagic events. The need for neuroimaging complicates the evaluation in the eyes of many practitioners but obtaining an initial study with a noncontrast head computerized tomography (CT) with appropriate fetal shielding or an magnetic resonance imaging (MRI) of the brain greatly facilitates diagnosis with minimal risk to the fetus.[13,14]

The primary treatment for ischemic stroke is administration of tissue plasminogen activator (tPA). However, pregnant patients were excluded from tPA clinical trials and there has been no systematic study of the treatment in this population. The major side effect of tPA in adults is hemorrhage including intracerebral hemorrhage. Concerns regarding the risks of tPA on the pregnant patient and fetus (eg, uterine hemorrhage, placental abruption, abortion, preterm delivery) have been raised but, with admittedly limited data, it appears that maternal mortality (1%), fetal loss (6%), and preterm delivery (6%) are all low.[15-17] It should be noted that some published reports include patients treated with earlier fibrinolytics, but the incidence of side effects with tPA does not appear significantly different. The large molecular weight of tPA (65 000 Daltons) likely precludes transfer across the placenta which limits direct effects on the fetus unless tied to maternal complications.[18,19] There is no dose adjustment or change in administration of the medication in pregnant patients (IV tPA dosing is 0.9 mg/kg administered using a 10% bolus over 1 minute followed by the remaining 90% over 1 hour). Treatment should be started within 3 hours after symptom onset. Although data from the European Cooperative Acute Stroke Study (ECASS) III suggests that the window can be extended to 4.5 hours, there are no reports of use of tPA in this extended time window in pregnant patients.[20] Interventional procedures such as thrombectomy or intraarterial lytics can also be considered for patients with large vessel thrombosis, but there is only anecdotal information related to safety or efficacy. Mechanical embolectomy has been performed on pregnant patients with pulmonary embolism which was felt to be life-saving for the mother but not without a moderate degree of fetal risk.[21]

Following the diagnosis of stroke it is important to evaluate the patient in a manner that reflects the presumed etiology of the infarct. This would often involve a transthoracic or transesophageal echocardiogram to evaluate for PFO and the possible presence of an intracardiac thrombus. A hypercoaguability panel is often performed but it is important to be aware that the results will need to be repeated several weeks following delivery given the coagulation pathway changes that exist in pregnancy.[4] Genetic testing for factor V Leiden and prothrombin gene mutation would not be altered by pregnancy. Low-dose aspirin for secondary prevention is felt to be safe during pregnancy with the caveat that, like most medications, antiplatelet agents have not been systematically studied early in pregnancy.[22] Women with known hypercoaguability disorders or who develop thrombi during pregnancy are generally treated with unfractionated or low-molecular weight heparin as these do not cross the placenta and confer no risk of teratogenicity or fetal hemorrhage in contrast to warfarin.

The overall incidence of hemorrhagic stroke in pregnancy is low and, much like ischemic stroke, occurs primarily in late pregnancy and in the puerperium. The incidence is similar to ischemic stroke but intracerebral hemorrhage has a higher maternal mortality rate and is estimated to account for 5% to 12% of overall maternal mortality during pregnancy.[4] Hemorrhage is primarily associated with preeclampsia / eclampsia, arteriovenous malformations (AVM, Figure 1), and cerebral aneurysm rupture but may also be secondary to a number of other causes that the hospitalist should consider.[23]

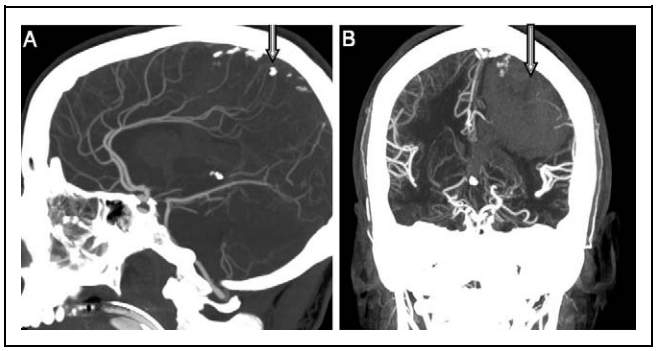

Figure 1. A ruptured arteriovenous malformations (AVM) in a 41-year-old woman in the 23rd week of pregnancy (with 4 previously uneventful deliveries). Calcifications are seen within the cortically based lesion (A). A large hematoma (B) displaces the left hemisphere.

One potential etiology for the increased risk of intracerebral hemorrhage (ICH) relates to the physiological changes of pregnancy including increased blood volume, rising blood pressure, and changes in vascular tone. The physical stress of labor and delivery may contribute to rupture risk, and patients with known aneurysms and AVMs are often delivered by scheduled C-section. It should be noted that the risk of vaginal delivery in these cases is unknown and may be equally low.[24] A patient with an intracerebral hemorrhage may present with a variety of symptoms but a sudden onset of a ''thunderclap'' headache is the classic description (see Table 1). Depressed level of consciousness and seizures are also common. The initial evaluation should include a noncontrast head CT which will identify a subarachnoid (often aneurysmal) or lobar (often AVM) hemorrhage. Subsequent angiographic imaging in an attempt to identify the source of the hemorrhage would then follow as this will dictate further therapy. If an aneurysm is identified during pregnancy repair is usually undertaken with neurosurgical clipping or endovascular coiling as this has been shown to reduce both maternal and fetal mortality.[24] Treatment of the patient in this setting should be guided by a team of neurosurgical, neurological, and obstetrical experts to best balance the mother's health and fetal viability. ICH in the setting of eclampsia, hypertension, or reversible cerebral vasoconstriction syndrome (RCVS) among other entities should be managed closely with antihypertensives and antiseizure medications including magnesium as appropriate.[11,25,26]

Cerebral Venous Thrombosis

Cerebral venous and sinus thrombosis (CVT) is a subtype of stroke which may result in ischemic and / or hemorrhagic complications. It is more common in women than in men ($\sim$3:1 ratio) and it is imperative that the neurohospitalist recognizes that pregnancy and the immediate postpartum period are associated with a significant increase in risk of cerebral venous thrombosis.[12] However, the overall risk of developing a CVT remains low in developed countries (11.6 per 100 000 pregnancies).[27] Mortality related to CVT is estimated at 9% and is primarily due to intracerebral hemorrhage.[28] The development of CVT has been related to a number of factors including hypercoaguable states, inflammatory disorders, and infection. Pregnancy, in and of itself, induces a degree of physiologic hypercoaguability in order to prepare for delivery and reduce the chance of maternal hemorrhage.[4,11] Other genetic causes of hypercoaguability including antiphospholipid syndrome, prothrombin gene mutations, and factor V Leiden / MHTFR deficiency are associated with the development of CVT.[29] Hypertension, caesarian section, infection, obesity, hyperemesis, dehydration, and prolonged bed rest may also further increase the risk of developing a thrombosis. In many patients, multiple risk factors are present and a single causal mechanism for the thrombosis formation may not be identified.[12] Women, although not pregnant women, may have exposure to oral contraceptive pills which have also been associated with an increased risk of developing CVT.[29,30] Neurohospitalists should have a high degree of suspicion and inquire about OCP use in any consult in young woman with headache and visual changes.[31]

The clinical syndrome related to CVT is quite variable and depends upon the territory of the affected vessel as described below.[32,33] Most commonly, the superior sagittal and transverse sinuses are affected and are associated with headache, seizures, and papilledema if severe enough to cause increased intracranial pressures. The cavernous sinus is less commonly affected and may present with cranial nerve deficits, headaches, proptosis, and painful opthalmoplegia related to increased pressure within the sinus and orbit. The deep structures of the brain, including the basal ganglia and thalamus, may be involved with occlusion of the deep cerebral veins resulting in focal neurological findings such as hemiparesis or aphasia.

Diagnosis of CVT can be challenging given the variable presentation and concerns regarding neuroimaging in the pregnant patient. Venous thrombosis often presents in a subacute fashion with symptoms such as headache which are not explored further until more dramatic symptoms demand attention (see Table 1). Examination of the patient suspected of having a venous thrombosis should include a complete neurological examination as well as a good fundoscopic examination to evaluate for papilledema.[34] If papilledema is identified, then cerebral imaging to evaluate for a source of increased intracranial pressure must be performed. Further treatment would then be guided by the findings on imaging. Lumbar puncture may be indicated as a therapeutic measure in patients with elevated ICP as long as imaging does not reveal a large intracranial mass lesion (including stroke or hemorrhage). Elevated D-dimer levels may help identify patients more likely to have CVT but levels below an identified threshold of 500 ng/mL do not rule out the diagnosis.[35,36] Severe cases of CVT may involve several vessels and result in ischemic infarctions and intracerebral hemorrhage. Venous infarcts related to CVT do not occur in the typical distributions

Table 1. Differential Diagnosis of "Thunderclap" Headache Presentations (Adapted From Table 3 Calabrese et al and Bousser et al)

Variable	RCVS	PACNS	SAH	Arterial Dissection	CVT
Sex	Female > Male, 2-3:1	No difference	Female > Male, 1.6:1	No difference	Female > Male, 3:1
Onset	Acute	Subacute/chronic	Acute	Acute or subacute	Subacute/chronic, can be acute
Headache	Severe/throbbing often thunderclap	Progressive/dull	prototypical thunderclap	Variable, can be thunderclap	Progressive / dull
CSF Findings	Normal or near normal	Abnormal in most	Abnormal RBC and or xanthochromia	Normal	Normal
Parenchymal brain imaging	May be normal Watershed infarcts or cortical SAH can be seen	Abnormal in most small infarctions in multiple distributions	SAH correlating to site and severity of arterial spasm. Stroke and edema may be present distally	Variable, may see ischemic stroke or vascular hematoma	Variable, may see ischemic stroke or hemorrhage
Neurovascular imaging	Areas of dilation and spasm intracranially in multiple distributions which are reversible by definition	Variable, often normal. Can see arterial irregularities in multiple distributions which may be irreversible	Saccular aneurysm or alternate source of bleeding. May see vasospasm peaking day 4-11	Vessel abnormalities (Flaps, double lumen, pseudoaneurysms)	Venous imaging (MRV or CTV) or venous phase conventional cerebral angiography may reveal vessel occlusion or areas of thrombosis

represented by arterial infarctions and this can be a clue that an underlying CVT is present. Some examples include midline infarctions and bilateral infarctions among others.[33] Magnetic resonance imaging of the brain is the best initial study to work up potential CVT in a pregnant patient as it does not require contrast administration and may also facilitate visualization of both the thrombus and the surrounding brain parenchyma.[37] This, often in conjunction with time-of-flight MRV imaging, may be diagnostic but can be difficult to interpret within the setting of thrombus evolution and partial recanalization (Figure 2). Noncontrast CT imaging which is often done in the ER setting, may reveal CVT but is less reliable than MRI.[38] A contrast-enhanced CT head and CT-venography (CTV) may provide detailed visualization of the venous sinuses although, as mentioned previously, the use of contrast material would not be the first choice in the pregnant patient.

Treatment of CVT in the nonpregnant population generally involves anticoagulation with warfarin to prevent clot extension. However, this is not an option in the first trimester (teratogenic) and is generally avoided later in pregnancy. The American Heart Association recommendations identify warfarin as safe in the second and third trimester, with the caveat that it must be discontinued late in the pregnancy in anticipation of delivery.[39] Low-dose aspirin is felt to be safe, particularly after the first trimester, per the American College of Chest Physicians 2008 guidelines.[40] Additionally, both groups suggest that unfractionated heparin or low-molecular weight heparin can be utilized in pregnancy either as a bridge to warfarin therapy or as a stand-alone treatment.[39,40] Following delivery, warfarin can be utilized for anticoagulation which is generally continued for a 3- to 6-month period with repeat imaging to establish the status of recanalization.

Interventional therapy utilizing thrombolytics or mechanical embolectomy are a consideration in severely affected patients who are not improving with systemic anticoagulation therapy. Two recent reviews examined the role of interventional treatment of CVT and reported mixed results.[41,42] Currently, there are no definitive randomized controlled studies to help guide management. In small series and case studies in aggregate, there is a trend toward favorable outcomes in severe cases of CVT that were treated with thrombolytics and/or thrombectomy.[41,42] Many of these studies include CVT patients with significant complications including ICH on systemic anticoagulation therapy and outcomes do not appear significantly different in this high-risk population.[41,42] Additionally, surgical decompression has been attempted in a small series of patients with elevated ICP related to CVT complicated by ICH[43] and represents a possible therapeutic option in severely affected patients. At this point, if interventional therapies are available and the patient is declining clinically, these should probably be considered, regardless of pregnancy status.

Eclampsia/Seizure

Preeclampsia is a complication of pregnancy that affects approximately 6% to 8% of pregnancies in developed nations.[44] It is a clinical syndrome defined by gestational hypertension and proteinuria which generally occurs after the 20th week of pregnancy (Table 2). Increasingly severe cases may be accompanied by symptoms including headache, visual changes, metabolic abnormalities, edema, and reduced fetal growth.[46,47] Development of these symptoms may also portend additional severe complications including hypertensive encephalopathy, intracerebral hemorrhage, pulmonary edema, renal failure, and other systemic failures.[47] The pathogenesis of preeclampsia / eclampsia is an area of active research and it is thought that complex interactions of placental, immune, and vascular factors throughout pregnancy lead to activation of maternal immune and cardiovascular systems and subsequent development of the clinical syndrome.[48,49]

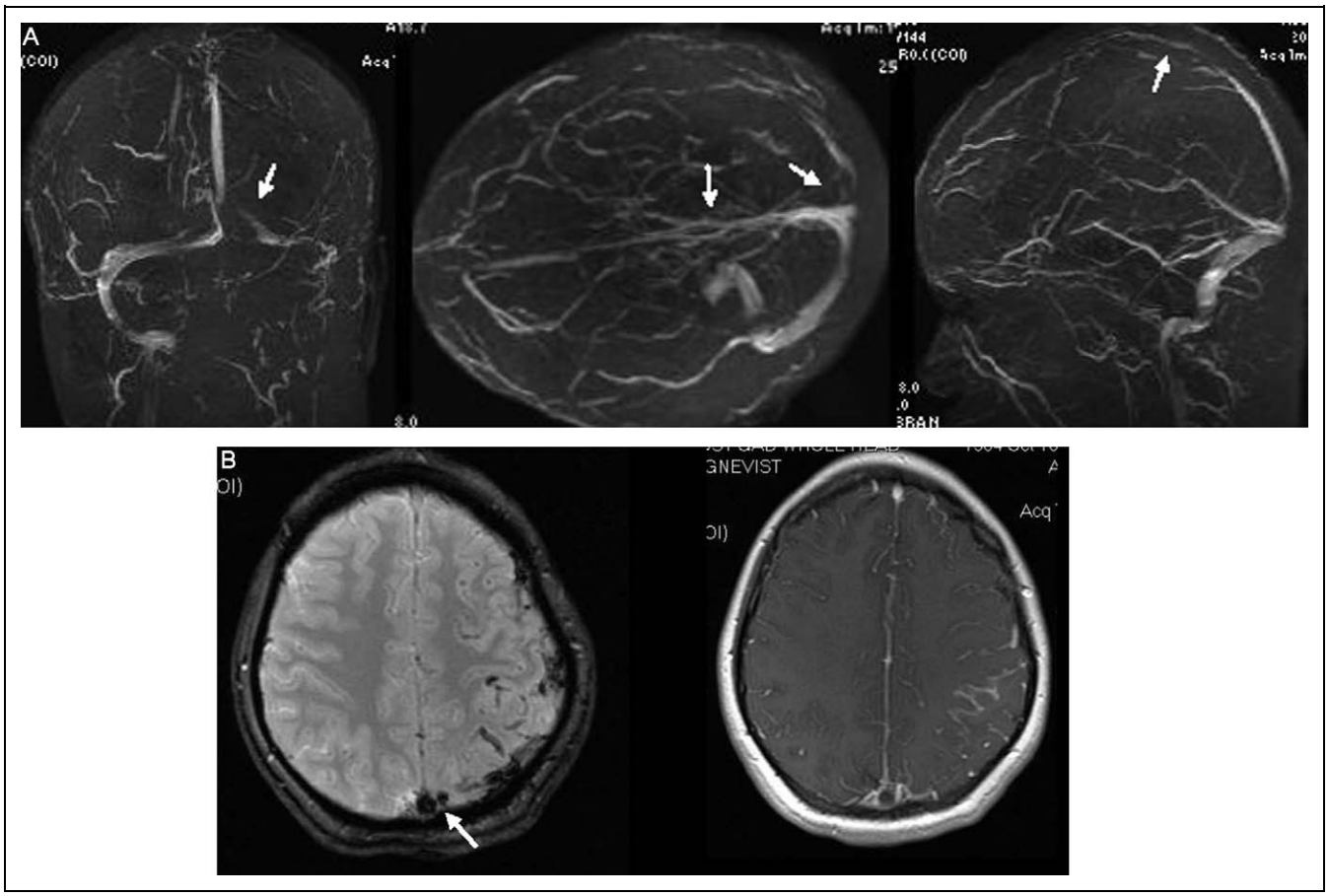

Figure 2. A, Left transverse sinus venous thrombosis with involvement of the jugular and sagittal vein in a woman 4 weeks postdelivery with an uncomplicated pregnancy. B, The same patient with cortical venous congestion and high signal in the superior sagittal sinus (Delta sign), apparent on magnetic resonance imaging (MRI) Gradient Imaging.

Eclampsia is traditionally defined as the addition of new onset seizures and/or coma during the pregnancy, labor, or peurperium in the setting of preeclampsia. Historically, it was felt that this represented a progression of the clinical syndrome, but more recent opinion suggests that seizures often occur in the absence of a preeclampsia syndrome, particularly in late postpartum eclampsia.[50] The diagnosis is primarily clinical (seizure) in the appropriate setting (see Tables 2 and 3). In patients who present early in the pregnancy (<21 weeks) or who present with prolonged altered mental status/coma or other neurological changes, additional testing may be warranted.[50] In the early presentation concern is raised for abnormal pregnancy (eg molar pregnancy) and with fulminate presentations care must be taken to fully evaluate for other disorders including acute stroke, hypertensive encephalopathy, and metabolic derangements (see Table 3).

Treatment of eclampsia and the associated seizure activity includes magnesium infusion, hypertension management, and supportive care.[25,46] If feasible, the obstetrics team will consider inducing delivery or performing a cesarean section as delivery is the most definitive "cure" for eclampsia. Basic seizure management, regardless of pregnancy status, involves supportive care (ABCs), maintaining the patient in a lateral decubitus position with suctioning as needed to reduce

Table 2. Causes of Seizures in Pregnancy Adapted From Kaplan[45]

Cerebrovascular causes	Cerebral infarction
	Intra-cerebral hemorrhage or aneurysm
	Cerebral venous thrombosis / hypercoaguability syndrome
	Reversible cerebral vasoconstriction syndrome
Hypertension	Cerebral edema and malignant hypertension
Structural abnormalities	Brain tumor, cerebral abscess, arterovenous malformations
Infections	Meningitis, encephalitis (HSV), fungal
Toxicity	Amphetamine, cocaine, theophylline, antipsychotics
Metabolic derangement	Hyponatremia, hyperglycemia, hypocalcemia
Epilepsy	

Table 3. Features of Preeclampsia and Eclampsia

Preeclampsia	Hypertension	Sustained SBP ≥ 140 mmHg Sustained DBP ≥ 90 mmHg Rise in SBP > 30 mmHg or DBP > 15 mmHg
	Proteinuria	Excretion of ≥ 300 mg every 24 hours Protein concentration of ≥ 100 mg/L (≥1+ dipstick)
	HELLP syndrome, hemolytic anemia, elevated liver profile, low platelets	Elevated liver enzymes and low platelet counts
Severe preeclampsia	Hypertension	Sustained SBP ≥ 160 mmHg Sustained DBP ≥ 110 mmHg
	Proteinuria	Excretion of ≥ 5 g every 24 hours Protein concentration of 5000 mg/L (3+ dipstick)
	Oliguria	Less than 500 mL of urine in 24 h
Eclampsia		Development of new onset generalized convulsive seizures and / or unexplained coma in a pregnant patient. May occur at any point including post-partum and may not be preceded by a clear pre-eclampsia syndrome.
Clinical symptoms	Any of the following	Headache, visual disturbances and perceptual deficits, upper abdominal pain, nausea and vomiting, shortness of breath Increased serum creatinine, thrombocytopenia, increased liver enzymes, pulmonary edema, fetal growth retardation

aspiration, supplemental oxygen, and insertion of padded bed rails to reduce injury from the seizure. While a single seizure is generally a self-limiting event, the potential for recurrent seizures pose a threat to mother and child. Magnesium sulfate is the first-line agent in obstetrical patients and, while the mechanism is not completely elucidated, may work through calcium channel receptors.[51] The treatment generally involves an initial bolus followed by a maintenance infusion until 24 hours following delivery or last seizure. Further seizures are treated with a bolus of magnesium sulfate or, if necessary to control recurrent events, additional agents such as amobarbitol[46,47] Hypertension is generally held to a range of systolic 140 to 160 using intravenous hydralazine or labetolol.[50] Additionally, oral nifedipine or IV nicardipine may also be of use in blood pressure management. Angiotensin-converting enzyme (ACE) inhibitors should be avoided due to potentially harmful effects on the fetal kidney.[52]

Reversible Cerebral Vasoconstriction Syndrome

Reversible cerebral vasoconstriction syndrome is a descriptive term which encompasses a variety of syndromes including postpartum angiopathy and puerperal vasospasm (see Tables 4 and 5). Reports have described the syndrome in association with a number of clinical settings including the postpartum state, migraine, hypertensive encephalopathy, and the use of vasoactive medications/drugs, among others.[53] Reversible cerebral vasoconstriction syndrome is predominantly a disease that affects younger patients with a mean age of onset 45 years and a slight female preponderance.[54] The epidemiology of RCVS is complicated by the variety of eponyms and incidence in pregnant and postpartum patients is uncertain. Similarly, the pathophysiology of RCVS is uncertain but the angiographic finding of vessel constriction and dilation suggests an alteration in cerebral tone.[53] Similar abnormalities have been described in reversible posterior leukoencephalopathy syndrome suggesting that there may be some shared mechanisms between these syndromes.[53,55]

Presentation is primarily characterized by acute-onset severe (thunderclap) headaches which may be accompanied by additional signs of neurological irritation including seizure,

Table 4. Reversible Cerebral Vasoconstriction Syndrome (RCVS) Synonyms

Call - Fleming syndrome
Cerebral pseudovasculitis
Postpartum angiopathy/puerpural vasospasm
Migrainous vasospasm/migraine angiitis
Benign cerebral vasculitis
Benign angiopathy of the central nervous system
Drug induced cerebral arteritis or angiopathy

Table 5. Reversible Cerebral Vasoconstriction Syndrome (Diagnostic Criteria Adapted From the 2004 International Headache Society Criteria and Those Suggested by Calabrese et al)

- Diffuse, severe headache (often "thunderclap" headache) of abrupt or progressive onset, with or without focal neurological deficits and/or seizures
- Exclusion of aneurysmal subarachnoid hemorrhage as etiology for presentation
- Normal or nearly normal CSF
- Evidence of segmental vasoconstriction ("string of beads", "sausaging") in the cerebral arteries via catheter angiography, CTA, or MRA
- Demonstrated "reversibility" of the vascular lesions within three months demonstrated by repeat angiography.

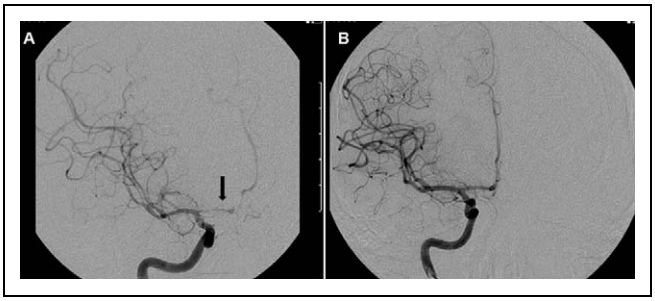

Figure 3. Reversible cerebral vasoconstriction syndrome (RCVS) in a woman 2 months postpartum. A 39-year-old who presented with severe onset of headache. Right anterior cerebral artery with segmental vasoconstriction (A) which resolved at the time of repeat imaging 2 months later (B).

stroke signs, and encephalopathy. The symptoms generally resolve over a period of 2 to 6 weeks and in the majority of patients the outcomes are good.[53,55,56] However, there are a subset of patients who experience severe spasm and resulting cerebral infarction, edema, and death.[53,54] The hallmark finding is the identification of reversible vasoconstriction of the cerebral arteries but it should be noted that vessel spasm is not always clearly identified which may add to diagnostic uncertainty. In pregnant and postpartum women, the most concerning differential diagnoses would include aneurysmal subarachnoid hemorrhage (SAH), ICH, pituitary apoplexy, venous sinus thrombosis. Additionally, while usually more subacute in onset, vascular spasm may be identified in cases of cerebral vasculitis.

Diagnosis of RCVS is based on the clinical syndrome and identification of vessel spasm on angiographic imaging (See Table 5 and Figure 3). Conventional cerebral angiography remains the standard imaging test given the increased resolution of the distal arterial tree. CT and MRI imaging may show evidence of border zone infarction and perfusion imaging may reveal hypoperfusion in the watershed regions distal to the affected arteries but may also be entirely normal.[57,58] Small high cortical areas of subarachnoid blood may also be visualized.[54] Further investigation in these patients is often undertaken to evaluate for systemic vasculitis and primary CNS vasculitis including serological studies and lumbar puncture to look for CSF inflammation and / or "CT-negative" SAH.[53] Lumbar puncture is not contraindicated by pregnancy or the postpartum state and a negative serological and CSF evaluation in the setting of a clinical story that fits with RCVS is helpful in directing therapy.

Treatment of RCVS is largely empirical and guided by experience in other clinical syndromes (SAH vasospasm, PACNS). Symptomatic management of the headache is addressed with analgesics including opiates. Calcium channel blockers (nimodipine or verapamil), magnesium sulfate, glucocorticoids, and cytotoxic agents have all been used in an effort to speed patient recovery.[26] The use of nimodipine stems from the aneurysmal SAH literature in which it has been effective in reducing the severity of vasospasm as well as potentially providing a neuroprotective effect.[26] Treatment with calcium channel blocker medications must be undertaken with caution as an excessive reduction in blood pressure may promote watershed brain ischemia distal to the affected arteries.[26] There has been conflicting results regarding the effect of magnesium sulfate but, like nimodipine, it appears to reduce the mobidity if not the actual incidence of vasospasm.[26] There is currently a study underway looking at magnesium sulfate treatment in aneurysmal SAH patients (IMASH trial), which may provide greater insight with regard to clinical benefit[59] in RCVS. Steroids and immunosuppressive agents are not generally utilized unless there is significant concern of an underlying vasculitic or inflammatory process

Posterior Reversible Encephalopathy Syndrome

Posterior reversible encephalopathy syndrome (PRES) involves a neurotoxic state most often characterized by headaches, confusion, seizures, and visual changes. Additionally, there are characteristic imaging features associated with the syndrome which often include focal regions of symmetric edema in the posterior brain parenchyma[60] (see Figure 4). The syndrome is described in a multitude of case reports and small clinical series but the incidence of PRES has not been clearly reported. As the case reports have accumulated, it has become clear that the associated imaging findings are neither uniform nor diagnostic and are not always reversible giving rise to a more multifaceted clinical syndrome than might be predicted given the descriptive name.[61-63]

The most common clinical manifestations of PRES include headaches, confusion, seizures, and visual changes. Onset may be acute or subacute, with symptoms developing over several days. Headache is generally reported to be moderate to severe in intensity with a diffuse quality.[64] Confusion is common and may progress to more significant degrees of altered awareness including stupor or coma. Seizures may start focally but often generalize and status epilepticus has been reported.[63,65] Finally, changes in vision including hemianopa, neglect, visual hallucinations or auras, and cortical blindness have all been reported.[60,65] In pregnancy, PRES generally develops in the setting of preeclampsia / eclampsia but may also develop in the puerperium and as a presenting feature of late-eclampsia.[66] Most patients do well if the seizures and hypertension are managed appropriately.[64] Unfortunately, some more severe cases can result in lasting neurological morbidity or mortality due to ischemic stroke or hemorrhage.[63]

The pathogenesis of PRES is unclear and controversial, but it is hypothesized that there may be an underlying disorder of cerebral autoregulation and / or endothelial dysfunction which can then be precipitated by metabolic derangements and drug exposures.[61]

In preeclampsia, the driving mechanism may be related to both of these hypotheses given the baseline state of diffuse endothelial activation and the presence of inflammatory

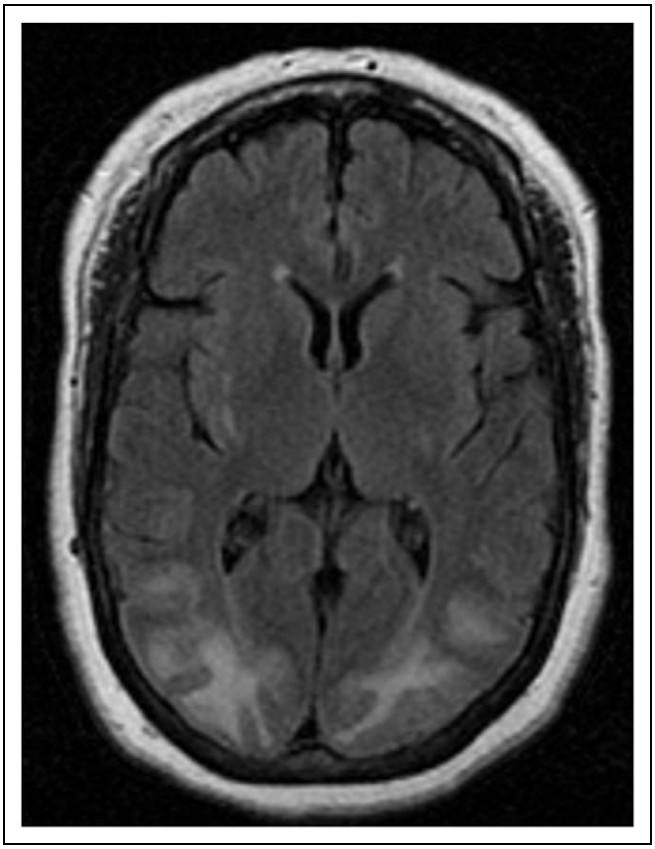

Figure 4. Symmetrical posterior edema on MRI T2 FLAIR images characteristic of posterior reversible encephalopathy syndrome (PRES) in a hypertensive pregnant woman who presented with visual changes (patches in her vision).

markers in pregnancy as well as a common finding of relative hypertension in affected patients.[61,63,67] It has been suggested that abnormal uteroplacental vasculature leads to underperfusion of the placenta with the subsequent release of vasoactive substances such as vascular endothelial growth factor (VEGF) into the maternal circulation.[49,67] Recent research has shown that exposure of cerebral vessels to plasma from preeclamptic women significantly increased blood brain barrier permeability, an effect that was blocked by administration of VEGF inhibitors.[67] It should be noted that although moderate-to-severe hypertension is a common feature of PRES, the syndrome can develop in normotensive patients without any history of acute changes in blood pressure.[68] There is likely some shared pathophysiology between hypertensive encephalopathy, PRES, and eclampsia, given the overlapping presentations and clinical findings.[13,69]

Diagnosis of PRES is greatly facilitated by neuroimaging as the typical finding of symmetrical leukoencephalopathy defines the classical syndrome in the setting of an appropriate clinical picture. In the archetypical presentation of PRES bilateral symmetrical areas of edema in the parietal-occipital regions are apparent on CT or MRI imaging. However, as evidenced by a number of case series over the years, the radiographic abnormalities may present asymmetrically and in other brain regions including the brainstem, basal ganglia, and cerebellum.[62,63] The distribution of the lesions usually involves multiple vascular territories that help to distinguish the changes from ischemic stroke. Resolution of the imaging findings is expected to occur over several weeks with corresponding resolution of the clinical syndrome.[64] Of note, the extent of the edema does not appear related to the severity of presentation or to the presumed precipitant.[63,68]

The treatment of PRES in the pregnant patient mirrors that of eclampsia and, as noted above, these may not represent distinct syndromes in the pregnant patient. The patients' obstetrician may consider emergent delivery if feasible and appropriate. Magnesium sulfate is often utilized for seizure control.[25] As with eclampsia, hypertension management is generally achieved with hydralazine or labetolol. If onset is associated with use of an immunosuppresive or chemotherapy medication, which would be unlikely in a pregnant patient, the offending agent is discontinued.

Neuropathies

Postpartum neuropathies are relatively uncommon and may lead to misdiagnosis and unnecessary work up. Intrinsic obstetric palsies are those attributed to the labor and delivery process itself. The incidence has dropped from 3.2% a century ago to less than 0.25% likely due to the shortened second stage of labor.[70,71] The most common injury is lateral femoral neuropathy, a purely sensory nerve from L2 and L4 innervating the anterolateral thigh, which can also occur during pregnancy itself, most frequently after 30 weeks of gestation. Palsies of the femoral, obturator, sciatic, common peroneal nerve, and lumbrosacral plexus also occur with decreasing frequency.[70] Most result from prolonged stretch or pressure in the dorsal lithotomy position but reports have suggested that nulliparity and prolonged second stage of labor are important risk factors.[70] Most importantly for the neurohospitalist seeing a postpartum patient is distinguishing this relatively benign condition from epidural injury, hematoma, or abscess secondary to obstetrical anesthesia.[70,72] Most injuries resolve by 6 to 8 weeks postpartum and can be confirmed with electromyography (EMG) if necessary.

Idiopathic Facial Nerve Palsy

Idiopathic peripheral facial nerve palsy or "Bell's Palsy" is the most common cause of unilateral acute facial paralysis, with an estimated incidence of 24 to 40 per 100 000 persons.[73] There is a female preponderance (2-4:1) regardless of pregnancy status, but the incidence may be up to 6-fold higher in pregnant women compared to nonpregnant women, although other studies have found no increase in incidence.[73-75] Regardless, when Bells' Palsy does occur during pregnancy, it most commonly presents during the third trimester or in the peripartum period.[74,75] The etiology of Bell's palsy does not appear to

be significantly different in pregnant women although there is an association with pre-eclampsia.[75,76] Treatment of Bell's Palsy with corticosteroids appears to be effective, but is often avoided in the first trimester due to potential adverse effects on the fetus.[75] Antiviral medications such as valacyclovir and famciclovir are pregnancy category B and may be of benefit if started within 3 days of onset of the facial paralysis in conjunction with corticosteroid therapy,[75,77] although the effectiveness of antiviral therapy has been debated for all patients with Bell's Palsy in a recent Cochrane review.[78] Recovery of motor activity has been studied by a number of groups and the available data suggests that the chance of full recovery is reduced in the pregnant patient.[73,75,79] However, these recovery rates must be taken in the context of the nontreatment bias that exists in the pregnant population.[73,75]

Guillian-Barré

Acute inflammatory demyelinating polyneuropathy (AIDP or Guillian-Barré syndrome; GBS) is a rare complication of pregnancy which, in a typical case, involves progressive motor weakness and areflexia.[80] In some cases, antecedent infection with *Campylopacter* jejuni or cytomegalovirus (CMV) can be identified and is associated with a more severe disease course.[80] CMV infection is important to identify as this may confer significant risk to the fetus via intrauterine transmission. The incidence of AIDP does not seem to rise during pregnancy but there may be an increased incidence in the immediate postpartum period, similar to what occurs in patients with multiple sclerosis.[80-82] Evaluation of suspected AIDP may involve spinal fluid evaluation with a characteristic finding of albuminocytologic dissociation (elevated protein level in the setting of an otherwise non-inflammatory sample), which can be performed safely in the pregnant patient. Nerve conduction studies may show a multifocal demyelenating polyneuropathy. However, it should be kept in mind that both of these studies may be normal in a small percentage of patients.[80] Treatment for AIDP does not differ in the pregnant population and both plasmapheresis and IVIG have been utilized.[80] Some authors suggest that treatment with IVIG may be slightly preferred given the fluid shifts and potential for clotting factor abnormalities that may complicate plasmapheresis treatment.[80,81] While the numbers are small, a case review by Chan et al did not identify treatment-induced fetal or maternal complications when used in the treatment of AIDP.[80] Additional considerations in the management of the AIDP patient include DVT prophylaxis and nosocomial infections including pneumonia and urinary tract infections.[80] AIDP does not appear to affect uterine contractile activity and delivery of the fetus in a patient with AIDP should be based on obstetrical indications.[80] Delivery should also be coordinated with anesthesiology as autonomic instability in some patients may complicate anesthetic care.[80] Additionally, there are reports of succinylcholine administration precipitating hyperkalemia and use should be avoided.[80,81]

Myasthenia Gravis

Myasthenia gravis (MG) is a chronic autoimmune disorder affecting neuromuscular transmission which results in fatigable weakness of the skeletal muscles. The muscles of the face and orbit in addition to the extremities can be affected. The prevalence of myasthenia gravis (MG) in the general population is estimated to be between 1:10 000 - 50 000. Women are more commonly affected (2:1).[83] The course of MG during pregnancy is variable and varies with subsequent pregnancies.[84] Exacerbations occur in approximately 40% of pregnancies with the remainder of patients experiencing stable disease or remission of symptoms.[83,85] Azathioprine can induce fetal leukopenia but is often maintained for severe disease. The management of preeclampsia in myasthenic patients presents a challenge as magnesium sulfate is contraindicated due to potential worsening of muscle weakness; and if seizures occur, Phenobarbital or Dilantin can be substituted.[83] Close consultation with the obstetrical team and anesthesiology team should dictate the manner of delivery and anesthetics utilized.[83] Vaginal delivery is not contraindicated but a myasthenic patient may not be able to tolerate full labor due to fatigue.[83] Following delivery, the infant must be closely evaluated for neonatal MG which occurs in approximately 10% to 20% of deliveries from placental transmission of acetylcholine antibodies and may be more prevalent in mothers who have not undergone thymectomy.[86] Symptoms of neonatal MG include poor sucking, generalized hypotonia, swallowing difficulties, and respiratory distress and generally responds well to anticholinesterase medications.[85] Pregnancy does not worsen the long-term prognosis of MG,[83] similar to what is observed in patients with multiple sclerosis.[82] It has been well-documented that autoimmune diseases often become quiescent during the latter stages of pregnancy, likely due to the restrained immune response to the pregnancy itself. The management of MS has been recently reviewed and will not be repeated here, but it appears that pregnancy has no long-term adverse consequences for patients with MS, and vice versa.[82,87] However, as in MG and AID, immunosuppressive therapies (except corticosteroids), interferons, and biological agents (antibody therapies) are relatively contraindicated in pregnant and breast-feeding women in an attempt to reduce fetal toxicity.[88]

Migraine

Headache is a common disorder among women of childbearing age. Migraine is 3 times more common in women (3:1 ratio) and female headache prevalence is highest during childbearing years.[89] However, studies have shown that the incidence of migraine headache is often reduced during the second 2 trimesters of pregnancy[89,90] Migraine has not been shown to significantly affect fertility or pregnancy outcomes, but it is associated with a risk of developing preeclampsia or stroke.[89,91] Headache diagnosis in pregnancy presents a challenge to practitioners as the headache may be related to

other etiologies requiring different management strategies. Primary headache syndromes common in pregnancy include migraine with or without aura and tension-type headaches[91,92] Secondary headache syndromes can be caused by a number of sources and often, but not always, are accompanied by changes in the neurological exam. These include infectious disease (ie, meningitis), vascular disease (stroke, CVT, SAH), idiopathic intracranial hypertension (IIH, aka pseudotumor cerebri), and preeclampsia/eclampsia.[92] New headache or significant change in headache pattern requires a full neurological/medical evaluation to ascertain the presence of a pathological secondary headache versus a more "benign" migraine or tension headache.[92] Focal neurological signs on examination, a fundal exam with papilledema, or concerning history such as fever, change in mental status, or seizure activity would direct the examiner toward a more urgent workup including imaging studies (trauma, vascular), laboratory work (infection, preeclampsia), and potentially CSF analysis and measurement of opening pressure (infection, IIH).[92]

Treatment of headache in pregnancy remains controversial due to concerns of potential detrimental effects of medication on the fetus. Many use a "wait-and-see" treatment philosophy given that headache frequency is often reduced later in pregnancy.[92] Unfortunately, many women continue to experience severe headaches throughout pregnancy and require treatment for pain as well as commonly associated symptoms such as nausea and vomiting.[91,92] The mainstay of preventing and treating migraine pain during pregnancy involves nonpharmacological methods including maintaining a consistent sleep schedule, stress management, regular meals, and remaining hydrated.[92] Additionally, studies have shown that biofeedback therapy and moderate consistent exercise can reduce headache pain and frequency.[92,93] Medical therapy is more limited in pregnancy but often include analgesics such as acetaminophen, steroids, and if necessary, opiate medications.[91] Adequate treatment of nausea can be instrumental in helping the patient maintain nutrition and hydration as well as facilitate sleep. Antiemetic therapy may include treatment with metoclopramide (may cause akisthesia, consider pretreatment with diphenhydramine, which may help abort migraine), ondansetron (does not particularly affect headache pain), and sedating agents such as promethazine and chlorpromazine (suppository formulations can be helpful in severely nauseated patients).[91,92] Triptans, a mainstay of acute migraine treatment in nonpregnant patients, are probably safe in pregnancy but may slightly affect preterm labor rates.[94] Unfortunately, given the limited safety data available, triptan therapy cannot be recommended.[91,94]

Diagnostic Considerations in the Pregnant Woman

Neuroimaging

Neuroimaging in pregnant women remains an area of controversy and some concern for most practitioners. However, neuroimaging in one form or another is both safe and feasible in most cases despite worries regarding the potential for long-term effects if the fetus is exposed to radiation or a strong magnetic field.[14] MRI is often the preferred imaging study for a pregnant patient as there is no radiation involved. Paramagnetic contrast agents are to be avoided however, as they cross the placenta with an unknown rate of clearance from the amniotic fluid.[95] The effects of gadolinium-based agents on the fetus are not understood, but limited data in animal models reveal potential teratogenicity.[95] However, the potential risk of imaging modalities must be balanced with the potential benefit obtained by facilitating rapid diagnosis.[96] MRI studies of the brain parenchyma can be very helpful in detecting both ischemic changes as well as hemorrhage depending on the series of sequences obtained. Additionally, by utilizing a focused panel of sequences aimed at a specific clinical question such as a limited stroke series (T2, FLAIR, DWI, and GRE) MRI time can be minimized without significantly compromising the utility of the study. Time-of-flight MR angiography, which does not require contrast administration, can be used to evaluate the cerebral vasculature.

During an imaging study in involving radiation, care must be taken to shield the fetus from radiation exposure as much as possible. However, American College of Radiology guidelines note that for diagnostic radiologic procedures outside of the abdomen /pelvis the radiation dose is characteristically very low as the fetus is exposed only to scattered radiation.[14] A plain head CT scan, which is widely available, exposes the fetus to approximately 0.5cGy of radiation which is about 1% of the accepted threshold for cumulative fetal exposure.[13] With regard to other commonly used diagnostic imaging modalities, there is essentially no formalized data regarding fetal safety when these technologies used to evaluate the brain. However, there are number of reviews looking at CT, CT angiography, and MRI in the thorax and abdomen which do not reveal significant trends in terms of fetal malformations or cognitive deficits.[96-98] In any imaging scenario, care should be taken to discuss the risks and benefits with the patient and to review the clinical picture with a radiologist who may be able to protocol the study to minimize fetal exposure. CT angiography and perfusion studies, which are increasingly utilized in a stroke evaluation, involve higher doses of radiation as well as the use of iodinated contrast and should be avoided unless deemed critical to the mother's evaluation. In the same vein, conventional cerebral angiography involves both radiation exposure and contrast administration but may, in some cases, be utilized as both a diagnostic and therapeutic intervention (eg aneurismal rupture, proximal cerebral embolism). Iodinated contrast is felt to be reasonably safe when utilized during pregnancy although there is a small concern related to induction of neonatal hypothyroidism.[97,98] Keeping the mother well hydrated and limiting the contrast dose given when possible are common strategies when it is felt that iodinated contrast use cannot be avoided.

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